Office Action Summary	Application No.	Applicant(s)	
	10/559,647	CROOKE ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,8-11,17,50 and 52-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *57-67* is/are allowed.

6)☒ Claim(s) *1,8-11,50,52 and 54-56* is/are rejected.

7)☒ Claim(s) *3, 6, 17, and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20090212* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 12/23/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 7/31/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 6, 8-11, 17, 50 and 52-67 are pending in the application.

Applicant's amendments filed on 12/23/08 have been considered and are convincing with regards to all pending rejections. Therefore, the rejections have been withdrawn. However, upon consideration of the instant claim amendments, a new ground(s) of rejection is made as explained below.

Priority

As explained in the office actions mailed on 5/14/07 and 11/15/07, applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No. 60/475,402 and Application No. 10/684,440, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The applications do not teach antisense compounds that are targeted specifically to the range of nucleotides "12380-13493" of instant SEQ ID NO: 4 and do not teach the sequence of instant SEQ ID NO: 87.

Therefore, the instant claims are accorded an effective filing date of 6/2/04, the filing date of PCT/US04/14540.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8-11, 50, 52, and 54-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Stinchcomb et al. (WO 96/09392), Nakamura et al. (WO 2004/031237 A1), Holen et al. (Nucleic Acids Research, 2002, Vol. 30, No. 8, pages 1757-1766), Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109), Baracchini et al. (US 5,801,154), and Ramasamy (US 6,525,191 B1).

It is noted that Baracchini et al. reference is of record and cited on the PTO-892 form mailed on 5/14/07; and the Elbashir et al., Stinchcomb et al., Holen et al., Olie et

al., and Ramasamy references are of record and cited on the PTO-892 mailed on 7/31/08.

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94%, 95%, or is 100% complementary to nucleotides 12380-12438 as set forth in SEQ ID NO: 4. The claims are directed to modifications, configurations thereof, length requirements, and stringency requirements between the antisense compound and the target nucleic acid.

It is noted that the instant rejection is strictly directed to double-stranded compounds. Recitation of single-strandedness in the claims, for example, would obviate this rejection.

Elbashir et al. teach that duplexes of 21-23 nucleotide RNAs are the sequence-specific mediators of RNA interference. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs are the most efficient triggers of sequence-specific mRNA degradation (see abstract). Elbashir et al. teach duplexes with overhangs as well as blunt ended duplexes that resulted in RNAi activity (see Figure 1, for example). Elbashir et al. teach duplexes wherein each strand is 19 nucleotides in length (see Figure 2, for example). Elbashir et al. teach that these elements provide a rational basis for the design of siRNAs in future gene targeting experiments (see abstract).

Elbashir et al. teach siRNAs wherein each strand is 20 nucleobases in length (see Fig. 2, for example). Elbashir et al. teaches siRNA molecules comprising 2'-deoxy modifications and unmodified RNA nucleotides that resulted in RNAi activity. Since the

siRNA molecules have more than one chemically distinct region, the siRNA molecules meet the instant limitation of being chimeric. Elbashir et al. teach that incorporation of 2'-deoxy substitutions did not affect RNAi, but help to reduce the cost of RNA synthesis and may enhance RNase resistance of the siRNA duplexes (see page 6885, column 1).

Elbashir et al. does not teach siRNAs directed to apolipoprotein (a) or the specific region of apo (a), as instantly recited. Elbashir et al. does not teach 2'-O-methoxyethyl, phosphorothioate, 5-methylcytosine, or bicyclic modifications, or combinations thereof.

Stinchcomb et al. teach an antisense compound, more specifically a ribozyme that is targeted to a sequence in human apo(a) that is 100% identical to nucleotides 12974-12988 of instant SEQ ID NO: 4 (see Table II on page 18 of Stinchcomb et al., ribozyme target sites of nucleotide positions 12453, 12481, 12592, 12650, 12974, 12976, 13119, 13226, and 13228). Stinchcomb et al. teach that incorporating chemical modifications into ribozymes prevents their degradation by serum ribonucleases (see page 12).

Nakamura et al. teach that the nucleotide sequence of siRNAs may be designed using a siRNA design computer program available from Ambion and teaches a protocol for selecting siRNA sequences. Nakamura et al. teach scanning the transcript beginning at the AUG codon for the presence of AA nucleotides to record potential siRNA target sites; comparing the potential target sites to the human genome database and eliminating target sequences with significant homology to other coding sequences using a BLAST search; and selecting qualifying target sequences for synthesis (see page 24).

Holen et al. teaches synthesis of several siRNAs against different sites on the same target mRNA, wherein the siRNAs demonstrated striking differences in silencing efficiency (see abstract). Holen et al. walked siRNAs in three nucleotide increments to determine the effect on silencing efficiency (see Figure 2), thus demonstrating that siRNA activity is routinely optimized by shifting target position across the mRNA sequence. The siRNAs resulted in varying activity, although each did result in silencing.

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity and teach compositions comprising the oligonucleotides with a pharmaceutical carrier. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides and specifically teach 2'-MOE modifications. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

Baracchini et al. teach antisense oligonucleotides with modifications such as phosphorothioates, 2'-O-methoxyethyl sugar moieties, and 5-methylcytosine nucleobase modifications (columns 6 and 7). Additionally, Baracchini et al. teach

chimeric oligonucleotides containing two or more chemically distinct regions (column 8). Baracchini et al. teach antisense oligonucleotides that it is preferable to target the coding region and for antisense oligonucleotides to be 8-30 nucleobases in length. Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al. teach that it is preferable for antisense oligonucleotides to be 100% complementary to the selected target.

Baracchini et al. teach that typically chimeric oligonucleotides are "gapped" oligonucleotides (or "gapmers") in which a region of deoxynucleotides (the "gap"), preferably containing at least four contiguous deoxynucleotides, is flanked by regions of modified nucleotides, preferably 2'-sugar modified nucleotides. In a preferred embodiment, the flanking regions (or "wings") contain 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy. In preferred embodiments the backbone may be phosphorothioate throughout or may be phosphodiester in the "wings" and phosphorothioate in the "gap". In other preferred embodiments, chimeric oligonucleotides may be "winged" oligonucleotides (or "wingmers" or hemichimeras) in which there is a deoxy "gap", preferably at least 4 contiguous deoxynucleotides, flanked on either the 5' or the 3' side by a region of modified nucleotides. Again, the flanking region (or "wing") preferably contains 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy and the backbone may be phosphorothioate throughout or may be phosphodiester in the "wing" and phosphorothioate in the "gap". Other

configurations of chimeric oligonucleotide are also comprehended by this invention. These may involve other modifications of the sugar, base or backbone, preferably in the oligonucleotide wing(s).

Ramasamy teaches bicyclic nucleic acid sugar moieties for antisense oligonucleotides and teaches that such moieties may have superior inhibitory properties.

It would have been obvious to design a siRNA, as taught by Elbashir et al., that is targeted to nucleotides 12380-12438 of instant SEQ ID NO: 4 and meeting the instant stringency requirements. It would have been obvious to incorporate the instant modifications and combinations/configurations of the modifications into the siRNA of Elbashir et al.

It would have been prima facie obvious to perform routine optimization to walk the known target sequence to design any given siRNA against the sequence in view of the guidelines taught by Elbashir et al., Nakamura et al., and Holen et al., as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular element used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. It was known in the art that the activity of a siRNA duplex can be optimized by shifting the target

sequence, as evidenced by Holen et al. and design guidelines were known in the art to determine optimal siRNAs, as evidenced by Elbashir et al. and Nakamura et al.

Since it was known to target instant SEQ ID NO: 4 with ribozymes, as evidenced by Stinchcomb et al., one would have been motivated to inhibit the expression of apo (a) with a siRNA as well, as it was known that siRNAs are used as potent inhibitors of target gene expression, as evidenced by Elbashir et al. and Nakamura et al. Therefore, it would simply be a matter of design choice to design a siRNA rather than a ribozyme, wherein the siRNA is directed to the same target sequence that had previously been targeted with ribozymes, as evidenced by Stinchcomb et al.

Furthermore, one would have been motivated to design the siRNA to have the structural characteristics set forth by Elbashir et al. because Elbashir et al. teaches guidelines and sets forth that the results provide a rational basis for the design of siRNAs.

With regards specifically to the siRNA being targeted to the instant region of SEQ ID NO: 4 and with the instant stringencies, siRNAs of this genus are within the genus that would result from routine optimization of the guidelines/testing set forth by Elbashir et al., Nakamura et al. and Holen et al. One would have been motivated to design siRNAs specific for human apo(a) via utilizing the rules of Nakamura et al. and Elbashir et al. and walking the target sequence as evidenced by Holen et al. Applicant has not demonstrated any unexpected result for the instant genus of siRNAs, wherein such sequences would have resulted from the rational design of siRNAs to apo(a) following the published guidance of Elbashir et al., Nakamura et al., and Holen et al.

In view of the availability of targeting guidelines, as taught by Nakamura et al., and the known optimization of siRNA duplexes via walking the target sequence, as evidenced by Holen et al., one of skill would have been able to envision every siRNA directed to the instant target apo (a) sequence. Although the relative activities would need to be experimentally determined, the majority of such siRNAs designed via the rules established in the art have some level of RNA interference activity.

As set forth in MPEP 2144.08, a species is obvious in view of the genus where one of skill would be able to immediately envision each species. Although the instant genus is large, one of skill would have been able to immediately envision each species of siRNA molecules targeted to apo (a) in view of the guidelines set forth by Nakamura et al. and readily available design algorithms. It would have been obvious to one of skill to select any given siRNA targeted to apo(a) based on the guidelines of Nakamura et al. and the optimization of Holen et al.

One would have been motivated to incorporate each of the instantly recited modifications because each of the modifications were known in the art to enhance the cellular uptake, enhance affinity for the nucleic acid target and increase stability of antisense oligonucleotides in the presence of nucleases, as evidenced by the combined teachings of Baracchini et al.. Olie et al., and Ramasamy. Since ribozymes, antisense oligonucleotides and siRNA molecules are each sequence specific inhibitory nucleic acid molecules that face delivery challenges in the cell, one would have been motivated to incorporate the modifications of Baracchini et al., Olie et al. and Ramasamy into the siRNA of Elbashir et al., which is further supported by the fact that Elbashir et al. does

incorporate modifications and teaches that modifications reduce cost and may enhance siRNA stability in the presence of RNases. Therefore, one would have certainly been motivated to try other modifications that were known to benefit antisense oligonucleotides in the siRNAs of Elbashir et al in order to optimize the activity therein.

Furthermore, one would have been motivated to incorporate combinations of the modifications as well as gapmer configurations, as Olie et al. teaches that such configurations resulted in increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity and to deliver nucleic acids in a composition with a carrier.

Finally, one of skill in the art would have had a reasonable expectation of success at generating a siRNA duplex that anticipates the instant genus because Stinchcomb et al. offers motivation to design inhibitory nucleic acids to the instant target and establishes apo(a) as a known target for sequence specific nucleic acid inhibitors, Elbashir et al. and Nakamura et al. teach design guidelines for siRNA molecules against any given mammalian target; and Holen et al. teaches walking a target sequence to optimize activity of the siRNA. Therefore, one would expect for the guidelines established by Elbashir et al., Nakamura et al. and Holen et al. to result in molecules

that would fall within the instant genus. Furthermore, Elbashir et al. teaches rational design guidelines for siRNA molecules including lengths and chemical modifications.

Therefore, one of skill in the art had the tools to aid and predict which siRNA molecules will have the required function, and can readily make and test the siRNAs for resultant RNAi activity, consistent with the published Written Description Guidelines (i.e. Example 12).

One would have had a reasonable expectation that the modifications and configurations thereof would benefit in the stability and delivery of the siRNA molecules of Elbashir et al. in view of the teachings of Olie et al., Ramasamy and Baracchini et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

It is noted that claims 3, 6, 17, 53, and 57-67 are not subject to the instant rejection under 35 USC 103(a) because claims are directed to antisense oligonucleotides, which are an embodiment of the instant antisense compounds that are single stranded.

Claims 3, 6, 17, and 53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 57-67 are allowed.

Conclusion

Claims 57-67 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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